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ORIGINAL ARTICLE

Value of copeptin and C-reactive protein in acute exacerbation of chronic obstructive pulmonary disease

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KEYWORDS

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Abstract *Objectives:* Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) describes the phenomenon of sudden worsening in airway function and respiratory symptoms in patients with COPD. The aim of this work is to study the value of copeptin and C-reactive protein in AECOPD.

Patients and methods: The study enrolled 31 patients with AECOPD and 10 control subjects. All patients were subjected to history taking, clinical examination, arterial blood gases analysis and sputum culture for bacteriological examination. Serum samples were obtained from the patients on admission, 3 days and 14 days after and from control subjects. The samples were analyzed for copeptin and CRP levels.

Results: The copeptin level on admission was significantly higher in AECOPD patients than the control subjects. The copeptin and CRP showed a statistically significant decline over the study duration but did not correlate with each other. ROC analysis curve showed that a copeptin level >14 pg/dl on admission had a sensitivity of 70% and specificity of 90% in predicting AECOPD and a level of >15 pg/dl on the fourteenth day had a sensitivity of 100% and specificity of 90% in predicting in-hospital mortality. Copeptin correlated significantly directly with the presence of bacterial infection and inversely with both PaO_2 and $PaCO_2$. Neither the copeptin nor CRP correlated with the COPD severity as expressed by the FEV_1%, BODE index and previous history of exacerbations.

Conclusion: Copeptin has a good sensitivity and excellent specificity in predicting AECOPD. Additionally, it has good predilection for short term outcome and in-hospital mortality.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the common health problems worldwide and in Egypt [1,2]. It is

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well accepted in the time being that COPD is not simply a local pulmonary disease but associated with systemic inflammatory process [3]. Acute exacerbation of COPD (AECOPD) describes the phenomenon of sudden worsening in airway function and respiratory symptoms in patients with COPD and contributes to the overall severity of the disease in individual patients [4]. Clinical judgment of the severity of the acute exacerbation is still the main reliable verdict. Various airway and systemic inflammatory markers are studied in both the stable and exacerbated phases of the disease [5,6]; and there is abundant evidence that both pan-airway and systemic inflammation are augmented in association with AECOPD [7]. C-reactive protein (CRP) is an acute-phase protein which rises in response to inflammation. Recently, there is an evidence that CRP is not just a marker of COPD but also contributes to pathogenesis and increases during AECOPD [8].

Copeptin, a 39-amino-acid-long peptide, is the C-terminal part of pro-arginine vasopressin and is released together with vasopressin during processing of the precursor peptide. Vasopressin, the antidiuretic hormone produced by the hypothalamus, is the key hormone involved in the hemodynamic and osmotic control and mirrors the individual stress level; but its instability precludes its routine use and makes reliable measurements difficult to achieve [9]. In contrast to vasopressin, copeptin is stable at room temperature in serum and plasma and can be measured as a 'shadow' fragment of vasopressin in the circulation [10]. the last years, copeptin was studied in a variety of clinical conditions, such as AECOPD, hemorrhagic and septic shock, myocardial infarction, heart failure and cerebrovascular stroke [11–14].

Objectives

The aim of this work is to study the value of copeptin and C-reactive protein in acute exacerbation of chronic obstructive pulmonary disease.

Patients and methods

Study design and population

A case control study enrolled 31 patients with acute exacerbation of COPD-attending the Chest Diseases Department of Alexandria Main University Hospital, Alexandria, Egypt-and 10 non-COPD participants with matched age and sex as a control group. All of the patients had a previous diagnosis of COPD according to the GOLD guideline [4] with a clinical evidence of exacerbation according to the previously accepted symptom-based definition [15]. Patients with evidence of confounding inflammatory diseases (such as malignancy, arthritis, connective tissue disorders or inflammatory bowel disease) or other pulmonary diseases (as asthma, tuberculosis or bronchiectasis) were excluded from the study. The study was approved by the local ethics committee and all participants signed an informed consent.

On admission, all of the patients were subjected to history taking, clinical examination, arterial blood gas analysis, plain chest X-ray, sputum culture for bacteriological examination and blood sample taking. After the initial evaluation of the studied group, the patients were managed according to the international guidelines. They were assigned to the standard drug protocol and supplemental oxygen therapy plus non-invasive ventilation (NIV). The standard drug protocol consisted of nebulized salbutamol (2 mg every 4 h), nebulized ipratropium bromide (500 μg every 6 h), corticosteroids (prednisolone 30 mg every day for a minimum of 5 days), aminophylline and an empirical antibiotic changeable after the antibiotic sensitivity testing if indicated. The administered fraction of inspired oxygen was adjusted to maintain arterial oxygen saturation values of 88–92%. Endotracheal intubation and invasive mechanical ventilation were introduced in case of failure of NIV trial. All of the patients were followed up for 14 days.

Inflammatory markers

Three serum samples were obtained from the patients: on admission, 3 days and 14 days after. A serum sample was also taken from the control subjects. All the samples were preserved in −80 °C till the end of the study period. The collected samples were analyzed for copeptin and CRP. The copeptin was measured by ELISA kit (Wuhan ElAab Science Co. Ltd, China) following the manufacturers' instructions. This immunoassay test allows for the in vitro quantitative determination of human copeptin concentrations in serum and plasma. The ELISA is based on the competitive binding enzyme immunoassay technique. The microtiter plate provided has been pre-coated with an antibody specific to copeptin. During the reaction, copeptin in the sample or standard competes with a fixed amount of biotin-labeled copeptin for sites on a pre-coated Monoclonal antibody specific to copeptin. Excess conjugate and unbound sample or standard are washed from the plate. Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. Then a TMB substrate solution is added to each well. The enzyme–substrate reaction is terminated by the addition of a sulfuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of copeptin in the samples is then determined by comparing the O.D. of the samples to the standard curve. No significant cross-reactivity or interference was observed.

Ultrasensitive-CRP was measured in serum samples by CRP-ultrasensitive (MICRO CRP/ ULTRA CRP, Vital Diagnostics, Italy). CRP was measured using the quantitative turbidimetric latex technique by Turbi-Quick® machine (Vital Diagnostics S.r.l. via Balzella 41/g/4, 47100 Forlì, Italy). Latex particles coated with specific anti-human CRP were agglutinated when mixed with serum samples containing CRP. The agglutination caused an absorbance change, dependent upon the CRP contents of the serum sample that can be quantified by comparison from a caliber of known CRP concentration. According to the manufacturers' directions, the latex was shaken gently and diluted in the following way (1 ml latex reagent + 14 ml diluent (1:15)). Also, the samples and controls were diluted in this way (50 μl sample or control + 450 μl NaCl 9 g/L (1:10)). From each prepared reagent, 500 μl was incubated in positions 1–4 in special cuvettes for at least 1 min, and then transferred in the reading channel. When requested in the display, 50 μl of the diluted sample was added. The results appeared automatically on the reader display after 240 s.

Statistics

All the data were presented as mean ± standard deviation (SD) or number and percentage (%) as appropriate. Comparisons between groups were performed using Mann–Whitney (for two independent groups) or Kruskal–Wallis tests (for three independent groups). The Spearman correlation coefficient (rho) test was used for the correlation between different parameters. The prognostic performance of CRP and copeptin predicts both the onset of exacerbation and the resolution of the event which were evaluated using Receiver Operating Characteristic (ROC) curve analysis. In a ROC curve the "sensitivity" is plotted against "100-specificity" for different cut-off points of each of CRP and copeptin. The area under the ROC curve (AUC) is a measure of how well each of CRP and copeptin can distinguish between two prognostic groups. The sensitivity, specificity, positive and negative predictive value of each marker were calculated accordingly. MedCalc® (version 9.2.1.0, Acacialaan 22, B-8400 Ostend, Belgium) was used for data analysis. All of the statistical tests used in the analysis were two sided where $p < 0.05$ was considered as significant. The 95% confidence interval (CI) has been shown.

Results

Study population

Table 1 shows the baseline characteristic data of the involved patients. The mean age of the patients was 56.6 ± 7.9 years, while that of the control group was 55.8 ± 4.6 years; with no statistical difference between the two groups. Twenty four (77.4%) patients were males and seven (22.6%) were females. The smoking index was 40.9 ± 22.5 where 35.5% of the COPD cases who presented with exacerbation were current smokers and 71% of the patients had a history of repeated exacerbation in the last year (⩾3/year). The enrolled patients were moderate to very severe COPD as showed in the spirometric test with an average BODE index of 5.3 ± 2.4 (Table 1). Bacteriological organism as a cause of exacerbation was identified in 61.2% of the recruited sputum samples.

Table 1 The characteristics of the patients.

Character	COPD Cases (n = 31)
Age; mean ± SD	56.6 ± 7.9
Gender (M/F); *n* (%)	24 (77.4%)/7 (22.6%)
Current smoker; *n* (%)	11 (35.5)
Smoking index; mean ± SD	40.9 ± 22.5
Dyspnea (MMRC); mean ± SD	2.7 ± 0.97
BMI (Kg/m^2); mean ± SD	28.01 ± 8.4
BODE index; mean ± SD	5.3 ± 2.4
History of repeated exacerbation (⩾3/year); *n* (%)	22 (71%)
Pulmonary function test	
FEV_1/FVC; mean ± SD	54.5 ± 11.9
FEV_1 (L); mean ± SD	1.22 ± 0.59
FEV_1%; mean ± SD	44.3 ± 19.6
FVC (L); mean ± SD	2.24 ± 0.97
FVC%; mean ± SD	60.3 ± 22.7
Arterial blood gases	
pH; mean ± SD	7.31 ± 0.06
PaO_2 (mmHg); mean ± SD	47.65 ± 13.3
$PaCO_2$ (mmHg); mean ± SD	69.5 ± 16.8
HCO_3 (mmol/L); mean ± SD	34 ± 7
SaO_2 (%); mean ± SD	74.5 ± 11.8

COPD, chronic obstructive lung disease; M, male; F, female; MMRC, modified medical research council dyspnea scale; BMI, Body mass index; Kg/m^2, kilogram/square meter; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; L, liter; pH, hydrogen ion concentration; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; SaO_2, oxygen saturation in arterial blood; HCO_3, bicarbonate level.

Serum inflammatory markers

The copeptin level on admission among the patients with AECOPD was significantly higher compared to the control group (20.7 ± 11.2 pg/dl vs. 11.4 ± 2.41 pg/dl respectively, $p = 0.0017$; Fig. 1A). The copeptin level showed a statistical significant difference over the study duration ($p = 0.011$; Fig. 1B); where it was higher on admission compared to the 3rd and 14th days (20.7 ± 11.2 pg/dl, 15.8 ± 5.4 pg/dl and 13.1 ± 2.7 pg/dl respectively). Additionally, the copeptin was statistically significantly lower on the 14th day compared to the admission day ($p = 0.005$); (Table 2). Similarly, the CRP showed a statistically significant change over the study duration ($p = 0.013$; Table 2); however, neither a significant decrease of its level after 14 days of AECOPD nor a significant correlation with the copeptin level have been encountered ($r = -0.085$, $p = 0.466$).

Using the Receiver Operating Characteristic (ROC) analysis curve, a copeptin level >14 pg/dl on admission had a sensitivity of 70% and specificity of 90% in predicting AECOPD (AUC = 0.842, 95% *CI* = 0.682 to 0.941, $p = 0.0001$; Fig. 2A) with 95% and 54% of positive and negative predictive values, respectively.

Correlations

On the third day after admission, the copeptin level had a statistically direct significant correlation with the presence of bacterial infection on admission ($r = 0.455$, $p = 0.033$; Fig. 3A) and an inverse correlation with PaO_2 ($r = -0.403$, $p = 0.044$; Fig. 3B). On the fourteenth day, the copeptin correlated significantly and inversely with $PaCO_2$ level on admission ($r = -0.520$, $p = 0.0147$; Fig. 3C). Neither the copeptin nor CRP correlated with the COPD severity as expressed by the FEV_1%, BODE index and previous history of exacerbations ($p > 0.05$).

Outcome

Among the AECOPD patients, 77.4% (24 patients) completed the study duration while 22.6% died (7 patients). The copeptin level was significantly higher among those who died compared to the survivors after 14 days (12.6 ± 2.3 vs. 18 ± 2.8 pg/dl, $p = 0.029$; Fig. 4); but not on admission nor after 3 days ($p > 0.05$; Fig. 4A). Using the ROC analysis, the copeptin level >15 pg/dl on the fourteenth day had a sensitivity of 100% and specificity of 90% in predicting in-hospital mortality (AUC = 0.976, 95% *CI* = 0.810 to 0.987, $p = 0.0001$; Fig. 2B) with 48.8% and 100% of positive and negative

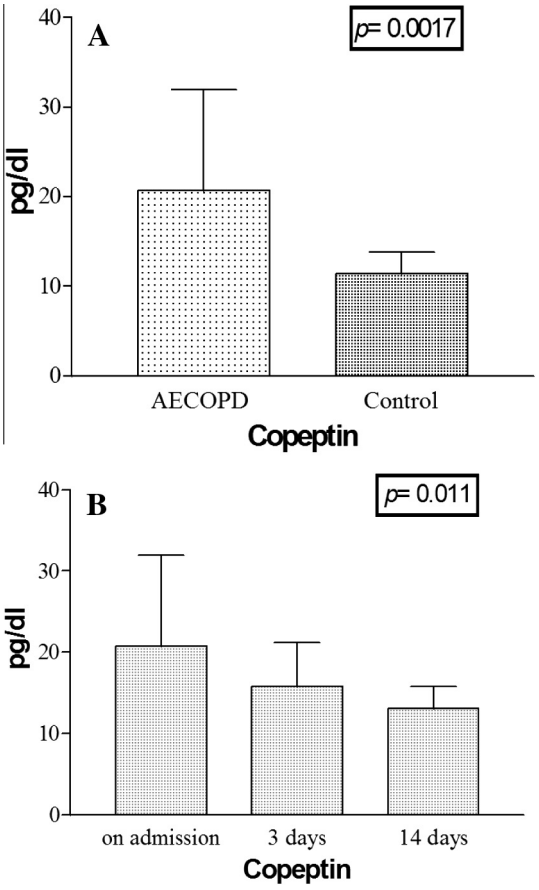

Figure 1 (A) Copeptin level comparison between AECOPD patients on admission and the control subjects; (B) Comparison between the levels of copeptin among the AECOPD patients over the study duration (admission day, after 3 days and after 14 days).

predictive values respectively. On the other hand, CRP had no similar significant difference between the survivors and the deceased patients despite being higher among the latter (Fig. 4B). However, on the fourteenth day, CRP level >2.5 mg/L had a sensitivity of 100% in predicting in-hospital mortality with a low specificity of 60% (AUC = 0.659, 95% *CI* = 0.439 to 0.838, $p = 0.472$).

Discussion

AECOPD is considered as the most common complication of COPD and is associated with accelerated decline in FEV_1 [16], poorer quality of life [17] and increased mortality [18]. However, the diagnosis of AECOPD is symptom-based [15]. Accordingly, various biomarkers have been evaluated in AECOPD in order to add an additional tool for the diagnosis of these events, predict their severity or mortality. In our study, we evaluated both copeptin and CRP as biomarkers of exacerbations and we assessed their value in the diagnosis of AECOPD and its outcome.

Stolz et al. [11] found in their study that copeptin was superior to CRP and procalcitonin in predicting the in-hospital outcome and length of hospital stay in patients with AECOPD as well as being significantly higher on hospital admission. Sharples et al. [19] found in their work that copeptin is significantly increased in bacterial infection. Another study reported higher copeptin level with increasing severity of lower respiratory tract infection and unfavorable outcome especially among patients with acute bronchitis and AECOPD [20]. Our results agreed with these studies; as we found that copeptin level on admission was significantly higher compared to control subjects and significantly changed over the course of the exacerbation. In addition, the copeptin after 14 days of exacerbation was significantly higher in patients who died during hospital stay. The copeptin level >15 pg/dl presented a sensitivity of 100% and specificity of 90% in predicting in-hospital mortality, rendering this biomarker extremely effective in predicting short term outcome of AECOPD.

In our study, in spite of its high sensitivity (up to 100%), CRP did not show significant relation to in-hospital mortality; a finding in agreement with that of Stolz et al [11]. This could be explained by the high sensitivity of the CRP which rises during infection or acute injury to just decline after vanishing of the initial stimulus rendering it a sensitive non-specific maker [21]. However, CRP showed a significant change over the duration of the study. This is attributed to the significant decrease after 3 days of therapy among the patients which could be secondary to corticosteroids used in the management of AECOPD [22], non-invasive ventilation [23] and the use of antibiotics which could modulate the systemic inflammatory response secondary to infection eradication.

Table 2 The biomarkers over the study duration.

Biomarker	Time			*p* Value
	On admission	On 3rd day	On 14th day	
Copeptin	20.7 ± 11.2 $z = 1.4$, $p = 0.162$ (1); $z = -1.913$, $p = 0.056$ (2); **$z = -2.785$, $p = 0.005$ (3)**	15.8 ± 5.4	13.1 ± 2.7	**$z = 8.963$ $p = 0.011$***
CRP	2.7 ± 1.04 **$z = 3.093$, $p = 0.002$** (1); $z = 1.07$, $p = 0.284$ (2); $z = -1.304$, $p = 0.192$ (3)	1.7 ± 1.2	2.13 ± 1.5	**$z = 8.624$ $p = 0.013$***

(1) Difference between admission and 3rd day values; (2) Difference between 3rd and 14th day's values; (3) Difference between admission and 14th day's values.

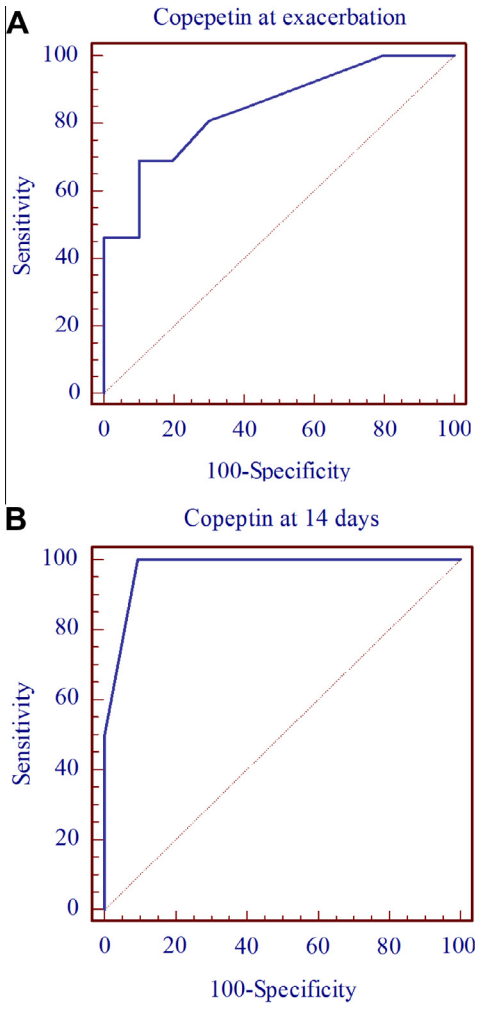

Figure 2 ROC for the copeptin. A: for predicting exacerbation (AUC = 0.976, 95% *CI* = 0.810 to 0.987, $p = 0.0001$), B: for predicting mortality (AUC = 0.842, 95% *CI* = 0.682 to 0.941, $p = 0.0001$).

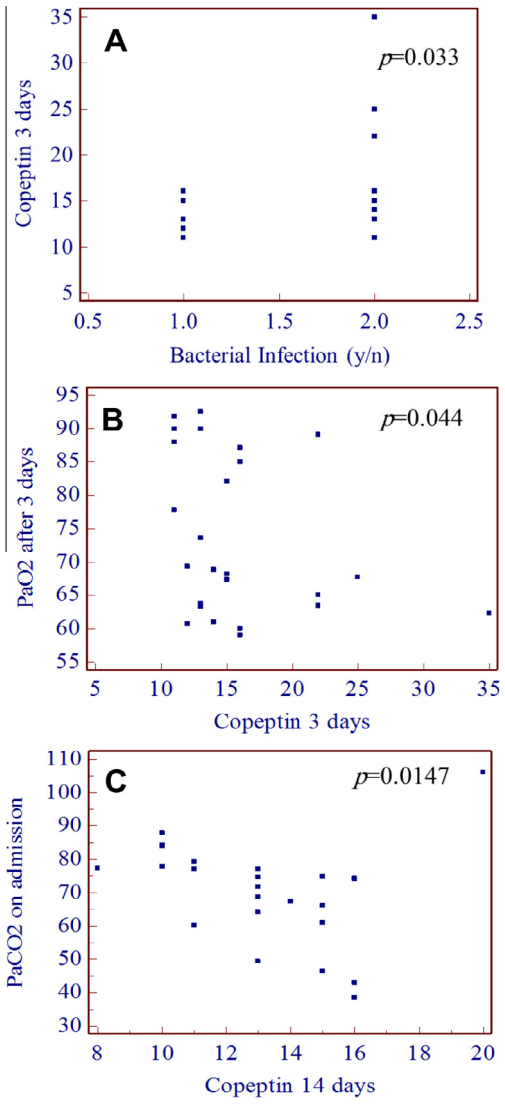

Figure 3 Correlations. (A) Copeptin after 3 days and the presence of bacterial infection; (B) Copeptin after 3 days and PaO_2 after 3 days; (C) Copeptin after 14 days and $PaCO_2$ on admission.

On the other hand, CRP increased after 14 days of exacerbation but did not reach a statistical significance. Indeed, Perera et al. [24] found an insignificant improvement of the CRP on the 14th day and on the 35th day of exacerbation which denoted persistent systemic inflammation post-exacerbation. They also speculated that a raised CRP concentration 14 days after exacerbation onset may be predictive of recurrence within the subsequent 50 days. Seemungal et al. [25] suggested that the inflammation can take months after the exacerbation episode to resolve.

Bacterial infection, as a cause of AECOPD, was identified in 61.2% of the cases falling within the percentages in previous publications [26]. Interestingly, the copeptin level after 3 days of acute event correlated directly with the presence of bacterial infection on admission. This could explain the persistence of higher copeptin level in those patients [20] and the non-significant change among the studied cohort (table 2) compared to a significant change after 14 days of therapy. Additionally, the copeptin correlated inversely with PaO_2 measured 3 days after the exacerbation. This finding was reported in previous publications which may be explained on the basis that vasopressin causes vasoconstriction which correlates to the hypoxia induced-vasoconstriction in severe COPD [27–29]. However we did not find any correlation between the copeptin level and the underlying severity of the COPD or the previous history of exacerbations. This was partially agreed by Stolz et al. [11] as they did not find correlation between the copeptin and FEV_1% but there was a trend for a positive correlation with a previous history of hospitalization secondary to AECOPD. This difference could be due to variability in the characteristics of the recruited patients as the majority of our patients were severe to very severe COPD and 71% have a repeated history of exacerbation in the last year. Nevertheless, Seligman et al. [30] found that copeptin increased in patients with critical care illness and correlated with the severity of the primary disease.

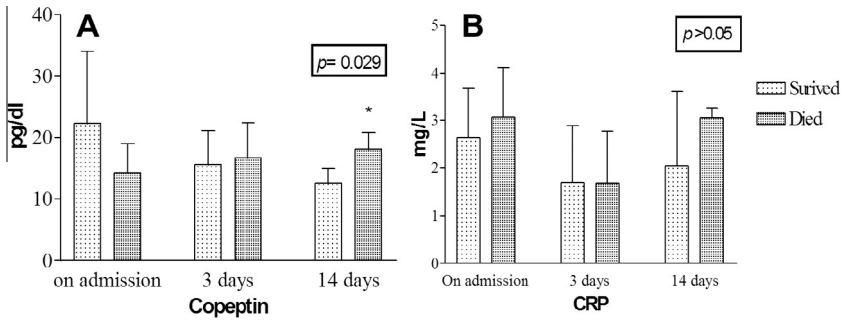

Figure 4 Comparison between the survived and dead patients over the study duration regarding copeptin levels (A) and CRP levels (B).

Conclusion

Copeptin is an acceptable biomarker aiding in the diagnosis of the AECOPD with a good sensitivity and excellent specificity in predicting AECOPD irrespective of the underlying severity of the disease. Additionally, copeptin could be used for following up the resolution of the exacerbation and short term outcome as it showed a good predilection of in-hospital mortality over CRP.

Conflict of interest

We have no conflict of interest to declare.

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